REMARKS

Claims 1-27 are pending in this application. Claims 1, 10, and 19 are amended herein. Applicant submits that support for the amendments is found throughout the specification, for example at page 5, lines 9-11, and at pages 12-15, and that no new matter is introduced herein.

I. Objections to the Specification

In the Office Action, the specification was objected to for referring to oligonucleotide 1 as a complement to the mdm-1 oncogene and as a complement to the mdm-2 oncogene.

The specification is amended herein as marked in Appendix A to correct the references to oligonucleotide 1 as a complement to the mdm-1 oncogene. Therefore, Applicant respectfully submits that this ground of rejection is overcome and should be reconsidered and withdrawn.

II. Nucleotide and/or Amino Acid Sequence Disclosure

The application was objected to for reciting sequence disclosures that were not referred to by the sequence identifier.

Applicant has amended the specification and claims as marked in Appendix A to comply with the sequence rules. Therefore, Applicant respectfully requests that this ground of rejection be reconsidered and withdrawn.

III. Claim Objections

Claim 19 was objected to for containing an inappropriate comma.

Claim 19 is amended herein to correct the punctuation error noted by the Examiner. Therefore, Applicant respectfully submits that this objection is overcome and should be reconsidered and withdrawn.

IV. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 10, and 19 stand rejected as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, claim 1 was rejected as being unclear as to whether the recited oligonucleotide sequence was being included or excluded in the claim.

Claim 1 is amended herein to clarify that the recited oligonucleotide sequence is excluded from the polyanions of the claimed invention. Therefore, Applicant respectfully submits that this ground of rejection is overcome and should be reconsidered and withdrawn.

Claims 1, 10, and 19 were rejected for failing to apprise one of ordinary skill in the art of the metes and bounds of the claim. Applicant respectfully submits that this ground of rejection is overcome herein by amendment in part and by traversal in part.

Claim 1, as amended, recites a method for potentiating the activity of a prodrug comprising co-administering a polyanion with the prodrug, provided that the polyanion is not an oligonucleotide having two 5′ and four 3′ 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1. Claim 1 no longer recites the phrase "without producing significant side effects."

Claim 10, as amended, recites a method for statistically significantly potentiating the activity of a prodrug, the method comprising co-administering a polyanion with the prodrug, wherein the polyanion is administered before the prodrug. Claim 10 no longer recites the phrase "without producing significant side effects."

Claim 19, as amended, recites a method for statistically significantly potentiating the activity of a prodrug comprising co-administering a polyanion with the prodrug, wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the polyanion. Claim 19 no longer recites the phrase "without producing significant side effects."

Applicant respectfully submits that the specification provides numerous examples of statistically significant potentiation of drug efficiency. In Example 1, the period by which survival of animals bearing tumors was extended was deemed to be statistically significant by employing an unpaired t-test. Exemplary p values deemed to be statistically significant using this model fell in the range of $p < 0.08$ to $p < 0.0001$. Thus, the specification provides adequate guidance for what values would be judged statistically significant, and what test was used to calculate those values. Therefore, one of skill in the art is apprised of the metes and bounds of the claim with regard to what values are considered to be statistically significant.

Accordingly, Applicant respectfully requests that this ground of rejection should be reconsidered and withdrawn.

V. Rejections under 35 U.S.C. § 112, first paragraph

Claims 10-18 and 19-27 stand rejected under 35 U.S.C. 112, first paragraph, because one of skill in the art would have to engage in trial and error experimentation

to develop methods of co-administering a prodrug with a phosphorothioate oligonucleotide without producing significant side effects.

The invention is directed to methods of potentiating the effectiveness of a prodrug , thus permitting the prodrug to be administered at a lower concentration and lessening the severity of side effects. However, solely to advance prosecution of the application, Applicant has amended claims 10 and 19 to no longer recite the phrase "without producing significant side effects."

In light of the amendment, Applicant respectfully requests that this ground of rejection be reconsidered and withdrawn.

VI. Rejections under 35 U.S.C. § 102 (b)

Claims 1, 10, and 19 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Wang, *et al.* (*Int. J. Oncol.* (1999) **15**:653-60). Applicant traverses this ground of rejectioni.

Claim 1 recites a method for statistically significantly potentiating the activity of a prodrug comprising co-administering a polyanion with the prodrug, wherein the polyanion is not an oligonucleotide having two 5′ and four 3′ 2′-O-methylribonucleosides and having the sequence of SEQ ID NO:1, which is complementary to the mdm-2 oncogene. Claims 2-9 depend from claim 1, and are directed to various embodiments of the method of claim 1, including the administration of anti-cancer prodrugs, specific agents, specific polyanions, and oligonucleotides comprising specific modified ribonucleosides.

Claim 10 recites a method for statistically significantly potentiating the activity of a prodrug comprising administering a polyanion with a prodrug, wherein the polyanion is administered before the prodrug. Claims 11-18 depend from claim 10, and are directed to various embodiments of the method of claim 10, including methods involving the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions, and oligonucleotides comprising specific modified ribonucleosides.

Claim 19 recites a method for statistically significantly potentiating the activity of a prodrug, comprising administering a polyanion with a prodrug, wherein the prodrug is administered at a concentration that would not be therapeutically effective in the absence of the prodrug. Claims 20-27 depend from claim 19, and are directed to various embodiments of the method of claim 19, including methods involving the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions, and oligonucleotides comprising specific modified ribonucleosides.

Wang *et al.* teaches a method for increasing the activity of a DNA damaging agent, HCPT, by administering an oligonucleotide complementary to the sequence of the multidrug resistance gene mdm-2. HCPT is an analog of the active compound camptothecin, but is not a prodrug. Wang *et al.* does not teach or suggest the statistical significance of the results obtained by co-administering the oligonucleotide with the DNA damaging agent. Furthermore, Wang *et al.* does not teach or suggest a method for increasing the activity of a prodrug by administering an oligonucleotide that does not have the sequence of SEQ ID NO:1.

Wang *et al.* also does not teach a method wherein a polyanion is administered prior to administration of a prodrug, or a method where a polyanion potentiates the activity of a prodrug at a concentration of the prodrug that is therapeutically ineffective in the absence of the polyanion.

Wang *et al.* does not teach each and every element of claim 1 because Wang *et al.* fails to teach a method for statistically significantly potentiating the activity of a prodrug. Furthermore, the only oligonucleotide taught to be effective by Wang *et al.* is specifically excluded from independent claim 1, and claims 2-9, which depend therefrom.

In the method recited in claim 10, the polyanion is administered prior to the administration of the prodrug. Because Wang *et al.* does not teach a method wherein a polyanion is administered prior to administration of a prodrug, Wang *et al.* does not teach the invention as claimed in independent claim 10, and in claims 11-18, which depend therefrom.

Because Wang *et al.* fails to teach the statistically significant potentiation of the activity of a prodrug at a concentration at which the prodrug would not be therapeutically effective in the absence of the polyanion, this reference does not the invention as claimed in independent claim 19, and in claims 20-27, which depend therefrom.

Accordingly, Applicant respectfully submits that as claims 1, 10, and 19 are not anticipated by Wang *et al.*, this ground of rejection is overcome and should be withdrawn.

VII. Rejections under 35 U.S.C. § 103

Claims 1-27 stand rejected as unpatentable over Tortora *et al.*, Wang *et al.*, Chen *et al.*, and Barrachini *et al.* Applicant traverses this ground of rejection.

Claim 1 recites a method for statistically significantly potentiating the activity of a prodrug comprising co-administering a polyanion with the prodrug, wherein the polyanion is not an oligonucleotide having two 5′ and four 3′ 2′-O-methylribonucleosides and does not have the sequence of SEQ ID NO:1. Claims 2-9, which depend from claim 1, are directed to various embodiments of the method of claim 1, including the administration of anti-cancer prodrugs, specific agents, specific polyanions, and oligonucleotides comprising specific modified ribonucleosides.

Claim 10 recites a method for statistically significantly potentiating the activity of a prodrug comprising administering a polyanion with a prodrug, wherein the polyanion is administered before the prodrug. Claims 11-18, which depend from claim 10 are directed to various embodiments of the method of claim 10, including methods involving the administration of anti-cancer prodrugs, specific prodrugs and prodrugs comprising specific agents, specific polyanions, and oligonucleotides comprising specific modified ribonucleosides.

Claim 19 recites a method for statistically significantly potentiating the activity of a prodrug, comprising administering a polyanion with a prodrug, wherein the prodrug is administered at a concentration that would not be therapeutically effective in the absence of the prodrug. Claims 20-27, which depend from claim 19 are directed to various embodiments of the method of the method of claim 19, including methods involving the administration of anti-cancer prodrugs, specific prodrugs, and prodrugs

comprising specific agents, specific polyanions, and oligonucleotides comprising specific modified ribonucleosides.

Tortora *et al.* teaches the synergistic effect observed when chemotherapeutic agents are administered prior to the administration of a sequence-specific oligonucleotide targeting the protein kinase A gene. The chemotherapeutic agents tested by Tortora *et al.* are not prodrugs. Furthermore, a control oligonucleotide, which was not a sequence-specific antisense oligonucleotide targeted to the protein kinase A gene, failed to potentiate the efficiency of the chemotherapeutic agents tested. Therefore, one of skill in the art would not predict that any oligonucleotide, antisense or otherwise, would potentiate the activity of a cytotoxic drug, but only that antisense oligonucleotides targeting the protein kinase A gene would do so. Tortora *et al.* does not teach methods of co-administering a polyanion and a prodrug where the polyanion is administered prior to administration of the prodrug. Furthermore, Tortora *et al.* does not teach the effect of administering a polyanion with a prodrug when the prodrug is administered at dose that is not therapeutically effective in the absence of a polyanion.

Wang *et al.*, as discussed herein, teaches a method for potentiating the activity of a chemotherapeutic agent, HCPT, by administering an antisense oligonucleotide targeting the multi-drug resistance gene, mdm-2. HCPT is not a prodrug. Therefore, Wang *et al.* does not teach or suggest a method for potentiating the activity of a prodrug by co-administering a polyanion and a prodrug. Wang *et al.* also fails to teach methods that involve the administration of a polyanion prior to the administration of a prodrug or methods that involve administering a prodrug at a dose that is therapeutically ineffective in the absence of a polyanion.

Chen *et al.* teaches antisense oligonucleotides targeted to the multi-drug resistance mdm-2 gene, and methods for potentiating the activity of the DNA-damaging agent HCPT. As discussed herein with respect to Wang *et al.*, HCPT is not a prodrug. Therefore, Chen *et al.* does not teach or suggest a method for potentiating the activity of a prodrug by co-administering a polyanion and a prodrug. Chen *et al.* also fails to teach methods that involve the administration of a polyanion prior to the administration of a prodrug or methods that involve administering a prodrug at a dose that is therapeutically ineffective.

Baracchini *et al.* teaches antisense oligonucleotides targeted to the multidrug resistance protein, and the use of these oligonucleotides to reverse resistance to chemotherapeutic agents. Barrachini *et al.* does not teach a method for potentiating the activity of a prodrug by co-administering a polyanion and a prodrug.

Neither Tortora, nor Wang, nor Chen, nor Baracchini, alone or in combination, provides a method for potentiating the activity of a prodrug by administering a polyanion in conjunction with the prodrug. One of skill in the relevant art would not have been motivated to potentiate the activity of a cytotoxic prodrug, such as CPT-11, with phosphorothioate oligonucleotides based on the teachings of Tortora, because Tortora does not teach a method for potentiating the activity of a prodrug, and because Tortora *et al.* teach that oligonucleotides that did not target the protein kinase A gene did not potentiate the activity of cytotoxic drugs.

Wang *et al.* does not compensate for the deficiencies of Tortora, *et al.* because Wang *et al.* similarly fails to teach the administration of a prodrug, and because Wang *et al.* teaches that an oligonucleotide that does not include the sequence of the mdm-2 gene did not potentiate the activity of the DNA-damaging agent HCPT. Similarly, the

teachings of Chen *et al.* are limited to the administration of oligonucleotides containing the sequence of the mdm-2 gene, and to the administration of HCPT, which is not a prodrug.

Baracchini *et al.* does not compensate for the deficiencies of Tortora *et al.*, Wang *et al.*, and Chen *et al.*, because Baracchini does not teach the potentiation of the activity of a prodrug or of any other agent by the administration of a polyanion. Therefore, the teachings of Tortora *et al.*, Wang *et al.*, Chen *et al.*, and Baracchini *et al.*, alone or in combination do not render the invention as claimed in independent claim 1 obvious. Therefore, Applicant respectfully submits that this ground of rejection is overcome and should be withdrawn.

Tortora *et al.*, Wang *et al.*, Chen *et al.*, and Barrachini *et al.* each fail to teach methods that involve the administration of a polyanion prior to the administration of a prodrug. Therefore, the teachings of these references, alone or in combination, do not render the invention as claimed in claim 10 obvious.

Tortora *et al.*, Wang *et al.*, Chen *et al.*, and Barrachini *et al.* fail to that the administration of a prodrug in combination with a polyanion can potentiate the activity of a prodrug such that a dosage that is therapeutically ineffective in the absence of the polyanion is therapeutically effective in the presence of the polyanion. Therefore, these references do not render obvious the invention as recited in claim 19.

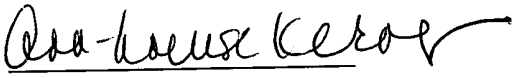
Accordingly, Applicant respectfully submits that as this combination of references does not render obvious the invention as recited in claims 1, 10, and 19, this ground of rejection is overcome and should be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully submits that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

This Amendment is being filed with a petition for a three-month extension of time, up to and including December 19, 2002. Applicant believes no other fees are due in connection with this Amendment. However, if there are any fees due, please charge them to Deposit Account 08-0219. Also, please credit any overpayment to the same Deposit Account.

Respectfully submitted,



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MARKED COPY OF AMENDED PARAGRAPHS AND CLAIMS

In the Specification:

At page 8, line 1 of the specification, please insert the following amended paragraph:

In certain preferred embodiments, an oligonucleotide for use in the invention may be complementary to an endogenous or exogenous nucleic acid sequence, preferably a nucleic acid that is involved in a disease. The term "complementary" means having the ability to hybridize to a genomic region, a gene, or an RNA transcript thereof under physiological conditions. Such hybridization is ordinarily the result of base-specific hydrogen bonding between complementary strands, preferably to form Watson-Crick or Hoogsteen base pairs, although other modes of hydrogen bonding, as well as base stacking, can also lead to hybridization. As a practical matter, such hybridization can be inferred from the observation of specific gene expression inhibition. The nucleic acid sequence to which the modified oligonucleotide sequence is complementary will depend upon the biological effect that is sought to be modified. In certain particularly preferred embodiments the oligonucleotide is complementary to a gene selected from mdm-2, PKA, PKC, raf-kinase, bcl-2, H-ras, c-myc, DNA methyltransferase, histone deacetylase, and VEGF. In certain preferred embodiments such an oligonucleotide has the sequence 5'-UGACACCTGTTCTCACUCAC-3' [SEQ ID NO: 1]. However, in other preferred embodiments oligonucleotides having this sequence are specifically excluded, and in some preferred embodiments oligonucleotides that are complementary to the mdm-2 gene are specifically excluded. In certain embodiments, antisense oligonucleotides are specifically excluded, as the

oligonucleotides used in the methods according to the invention are capable of potentiating the activity of prodrugs in a sequence independent manner.

At page 12, line 3 of the specification, please insert the following amended paragraph:

Female nude NC-r nude mice, 6-8 weeks of age, were fed *ad libitum* water (reverse osmosis, 0.17% Cl) and an autoclaved standard rodent diet (NIH31) of 18% protein, 5% fat, 5% fiber, 8% ash, and 3% minerals. Mice were housed in microisolators on a 12 hour light cycle at 22°C in 40-60% humidity. Mice were implanted subcutaneously in the flank with 1 mm HCT-116 human colon carcinoma fragments in the flank. Tumors were monitored twice weekly initially, then daily as the tumors reached approximately 100 mg in weight. When the tumors reached a weight between 40-221 mg (calculated weight), the animals were pair-matched into the various treatment groups. Estimated tumor weight was determined according to the equation: tumor weight =

$$\frac{w2 \times l}{2}$$

where w = width and l = length in mm of a HCT-116 tumor. Phosphorothioate oligonucleotides having 2'-O-methylribonucleotides at the 2 terminal 5' positions and 4 terminal 3' positions (oligo 1) or the 4 terminal 5' and 3' positions (oligo 2) were prepared according to standard procedures and dissolved in neutral buffered saline. Oligo 1 had the sequence 5'-UGACACCTGTTCTCACUCAC-3' [SEQ ID NO: 1] (complementary to mdm-2), and the sequence of Oligo 2 was 5' UCGCACCCATCTCTCTCCUUC3' [SEQ ID NO:2] (complementary to the HIV-1 gag gene). Camptosar was purchased from Pharmacia & Upjohn.

At page 14, line 14 of the specification, please insert the following amended paragraph:

A3

Comparison of the potentiation of Camptosar efficiency by Oligo 1 against potentiation of Camptosar efficiency by Oligo 2 shows that there is a stastically significant difference in favor of Oligo 1 ($p < 0.0074$; unpaired t-test). It is believed that this difference may arise from an antisense effect of Oligo 1 on expression of the [mdm-1] mdm-2 oncogene to which it is complementary.

At page 14, line 23 of the specification, please insert the following paragraph:

A4

To test whether the differences between Oligo 1 and Oligo 2 resulted from an antisense effect by Oligo 1, similar studies were conducted in a mouse model for pancreatic cancer (Panc 1 tumor). The Panc 1 tumor has a mutant (nonfunctional) p53 gene. Since antisense effects against [mdm-1] mdm-2 are believed to work primarily by upregulating p53 expression, Oligo 1 should not produce an antisense specific effect in this model. However, it is possible that mdm-2 targeted oligonucleotides in p53 mutant cell lines may work by a mechanism independent of p53.

At page 15, line 3 of the specification, please insert the following paragraph:

A5

The study was carried out as described in Example 1, except that Panc-1 tumor was used, 4 groups of 10 mice each were used, Oligo 1 and Oligo 2 (in this case, 5′ UCCCACCTATTCTTACUCCC3′ [SEQ ID NO: 3], with two 5′-terminal 2′-O-methylribonucleosides and four 3′-terminal-2′-O-methylribonucleosides) were given at doses of 20 mg/kg, Camptosar was given at 100 mg/kg, tumor "cut-off" was 1.2 g, and the study was terminated on day 67.

In the claims:

1. A method for statistically significantly potentiating the activity of a prodrug [without producing significant side effects], the method comprising co-administering a polyanion with the prodrug, wherein the polyanion is not an oligonucleotide having two 5′ and four 3′ 2-O-methylribonucleosides and wherein the oligonucleotide does not have [having] the sequence of SEQ ID NO: 1 [5′-UGACACCTGTTCTCACUCAC3′].

10. A method for statistically significantly potentiating the activity of a prodrug [without producing significant side effects], the method comprising co-administering a polyanion with the prodrug, wherein the polyanion is administered before the prodrug.

19. A method for statistically significantly potentiating the activity of a prodrug [without producing significant side effects], the method comprising co-administering a polyanion with the prodrug,[,] wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the polyanion.